



## General

### Guideline Title

ACR Appropriateness Criteria® fever without source or unknown origin — child.

### Bibliographic Source(s)

Westra SJ, Karmazyn BK, Alazraki AL, Dempsey ME, Dillman JR, Garber M, Moore SG, Raske ME, Rice HE, Rigsby CK, Safdar N, Simoneaux SF, Strouse PJ, Trout AT, Wotton-Gorges SL, Coley BD, Expert Panel on Pediatric Imaging. ACR Appropriateness Criteria® fever without source or unknown origin - child. Reston (VA): American College of Radiology (ACR); 2015. 12 p. [79 references]

### Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Coley BD, Karmazyn B, Binkovitz LA, Bulas D, Dory CE, Garber M, Hayes LL, Keller MS, Meyer JS, Milla SS, Paidas C, Expert Panel on Pediatric Imaging. ACR Appropriateness Criteria® fever without source - child. [online publication]. Reston (VA): American College of Radiology (ACR); 2011. 9 p. [79 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Recommendations

### Major Recommendations

ACR Appropriateness Criteria®

Clinical Condition: Fever without Source or Unknown Origin — Child

Variant 1: Neonate younger than 1 month of age with fever without source (FWS) and no respiratory symptoms.

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	5	This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.	<input type="text"/>
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation

Radiologic Procedure	Rating	Comments	Level RRL*
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Variant 2: Neonate younger than 1 month of age with FWS and respiratory symptoms.

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	8		<input type="text"/>
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Variant 3: Infant or child aged 1 to 36 months with FWS with low risk for occult pneumonia (no respiratory signs or symptoms, fever  $<39^{\circ}\text{C}$ , leukocytosis  $<20,000/\text{mm}^3$ ).

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	2		<input type="text"/>
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Variant 4: Infant or child age 1 to 36 months with FWS with any of the following: respiratory signs or symptoms, or fever  $\geq 39^{\circ}\text{C}$  or white blood cell count  $\geq 20,000/\text{mm}^3$ .

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	9		<input type="text"/>
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Variant 5: Child with FWS and neutropenia.

Radiologic Procedure	Rating	Comments	RRL*
CT chest with contrast	6	This procedure may be appropriate if patient has respiratory symptoms or has had stem cell transplant.	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
X-ray chest	5	This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating. This procedure may be appropriate if patient has respiratory symptoms.	<input type="text"/>
CT chest without contrast	5	This procedure may be appropriate if patient has respiratory symptoms or has had stem cell transplant.	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative

Radiologic Procedure	Rating	Comments	RRL*
CT abdomen with contrast	5	Consider in patients who have had stem cell transplant.	<input type="text"/>
			<input type="text"/>
			<input type="text"/>
CT paranasal sinuses with contrast	4	Contrast and brain imaging are essential if central nervous system invasion is a concern.	<input type="text"/>
			<input type="text"/>
CT paranasal sinuses without contrast	4	Consider in patients who have had stem cell transplant.	<input type="text"/>
			<input type="text"/>
CT abdomen without contrast	2		<input type="text"/>
			<input type="text"/>
CT chest without and with contrast	1		<input type="text"/>
			<input type="text"/>
CT abdomen without and with contrast	1		<input type="text"/>
			<input type="text"/>
CT paranasal sinuses without and with contrast	1		<input type="text"/>
			<input type="text"/>
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 6: Infant or child more than 1 month of age with fever of unknown origin (FUO).

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	7		<input type="text"/>
US abdomen	6		O
CT chest with contrast	5		<input type="text"/>
			<input type="text"/>
CT chest without contrast	4		<input type="text"/>
			<input type="text"/>
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative

CT abdomen with contrast Radiologic Procedure	4 Rating	Comments	RRL*
			<input type="text"/> <input type="text"/> <input type="text"/>
CT paranasal sinuses without contrast	4		<input type="text"/> <input type="text"/> <input type="text"/>
FDG-PET/CT skull base to mid-thigh	4	This procedure should not be used as the initial study. Consider if extensive clinical and imaging workup is negative.	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
CT paranasal sinuses with contrast	3		<input type="text"/> <input type="text"/> <input type="text"/>
MRI whole body without contrast	3		O
CT abdomen without contrast	2		<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
MRI whole body without and with contrast	2	This procedure should not be used as the initial study. Consider if extensive clinical and imaging workup is negative.	O
CT chest without and with contrast	1		<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
CT abdomen without and with contrast	1		<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
CT paranasal sinuses without and with contrast	1		<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

#### Summary of Literature Review

#### Introduction/Background

The febrile pediatric patient, especially an infant, represents a dilemma for the primary care physician. The definition of fever is generally regarded as a rectal temperature of  $\geq 38^{\circ}\text{C}$ . Oral temperatures are less reliable in infants and young children, although they are the usual method of measuring temperature in older children and adults. The cause of fever in the pediatric patient can often be determined from the history, physical

examination, and laboratory tests. Prior medical conditions, medications, foreign travel, and immunization history are all important in directing subsequent investigations. However, 20% of cases will have no apparent source and thus are defined as having fever without source (FWS). FWS is therefore defined as an acute illness in which the origin of the fever is not apparent after initial careful history and examination. Most FWS are caused by infections. The approach to a febrile child is generally divided into the infant younger than 3 months and the older infant and child between 3 and 36 months of age. Infants younger than 1 month deserve more aggressive evaluation because these children have more immature immune systems, are more difficult to evaluate, and do not have the protection afforded by the *Haemophilus influenzae* (*H. flu*) and *Streptococcus pneumoniae* (*S. pneumonia*) vaccines.

Although FWS is mostly self-limited and of little clinical concern, the burden on clinicians is to decide which children actually have a serious bacterial infection (SBI) that requires antibiotic treatment and even hospitalization. Febrile neonates are at higher risk; the reported incidence of SBI in all febrile neonates presenting to emergency departments varies between 6% and 28%. In children, the usual sources/causes of SBI are urinary tract infection, pneumonia, bloodstream infection, and meningitis. With the advent of vaccines for the most common pathogenic serotypes of *H. flu* and *S. pneumonia*, the incidence of SBI has dropped significantly. Although it is implied by the definition of FWS that the etiology of fever is unknown, many studies and guidelines include children with respiratory symptoms. For this reason, the guideline authors were compelled to include in their guidelines for FWS children with respiratory symptoms.

Although the terms are sometimes used interchangeably, FWS is different from fever of unknown origin (FUO). Pediatric FUO refers to a fever of  $\geq 38.3^{\circ}\text{C}$  with no apparent diagnosis after initial outpatient or hospital evaluation that includes a careful history and physical exam and initial laboratory assessment. There is much variability in published studies of FUO, with required duration of fever ranging from 1 to 3 weeks. The majority of children with FUO have infectious causes, although inflammatory, neoplastic, and autoimmune conditions are also in the differential. The distinction between FWS and FUO is more than just academic because the clinical and imaging approaches to these conditions can differ.

## Overview of Imaging Modalities

A detailed and thorough history and physical examination is the most important component of the diagnostic evaluation of a child with FWS or FUO. Chest radiographs have a role in evaluation of occult pneumonia and should be performed in neonates with FWS and respiratory symptoms and in selected older children with high fever, leukocytosis, and respiratory signs and symptoms. However, chest radiographs are limited in evaluation of pneumonia in young children due to poor differentiation between viral and bacterial pneumonia and considerable intraobserver and interobserver variability in interpretation. Computed tomography (CT) of the paranasal sinus, chest, and abdomen are important for evaluation of fungal infection in neutropenic patients, especially after bone marrow transplantation, and in patients who do not respond to broad-spectrum antibiotics. There are small series on the use of fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET)/CT in evaluation of FUO that show its potential to detect occult infection, inflammatory processes, and malignancy. It can be used in selected children with FUO with negative extensive workup.

## Discussion of Imaging Modalities by Variant

### *Variants 1 and 2: Neonate Younger Than 1 Month of Age with FWS*

In febrile neonates younger than 28 days, history and physical examination alone may not be able to completely exclude SBI, even in children who appear clinically well or mildly ill. Therefore, a full sepsis workup is frequently performed. This includes complete blood count, blood culture, urinalysis and urine culture, lumbar puncture with evaluation of cerebrospinal fluid, and administration of antibiotics in the emergency department, followed by hospitalization pending results of cultures.

A chest radiograph is indicated in neonates with FWS and respiratory symptoms. In addition, a chest radiograph in a septic-appearing neonate with FWS may disclose an occult pneumonia. Some investigators advocate routine chest radiographs in all neonates with FWS because these infants are relatively immunocompromised compared with older infants and children, and the consequences of a missed SBI or occult infection are felt to be greater. A chest radiograph can help exclude congenital or acquired cardiac disease in a child who is febrile and ill. However, the benefit of routine use of chest radiography in neonates without respiratory symptoms has not been established.

### *Variant 3: Infant or Child Aged 1 to 36 Months with FWS with Low Risk for Occult Pneumonia (No Respiratory Signs or Symptoms, Fever $<39^{\circ}\text{C}$ , Leukocytosis $<20,000/\text{mm}^3$ )*

In the absence of a "toxic" appearance, respiratory distress, poor peripheral perfusion, high fever, and leukocytosis, the risk for SBI is low in children with FWS and there is no indication for routine chest radiography. One group of researchers retrospectively studied 105 infants who had fever. Of the 37 patients who had no respiratory symptoms or signs, only one had chest radiograph showing a focal parenchymal airspace disease. Hyperinflation and peribronchial thickening were not classified as abnormal. In a prospective study, the same authors included 121 infants who were free of signs or symptoms of lower respiratory tract infection but who had fever. None had chest radiographs that showed an abnormality. Even in younger children at the age of 1 to 3 months that are of increased risk of SBI, there is no role of routine chest radiography. Another group

of authors showed that only 6% of infants with fever without respiratory manifestations developed pneumonia and that all of those infants did well. A meta-analysis of 361 febrile infants younger than 3 months without clinical evidence of pulmonary disease on history or physical examination showed that none of these children had pneumonia. Another study reported a 3.3% incidence of positive chest radiographs based on collected reviews of infants and children from birth to 36 months of age with fever and no respiratory symptoms or signs. Another author, summarizing a number of clinical series dealing with acute episodes of fever in infants, also believes that chest radiographs should be obtained only when there are clinical symptoms or signs of pneumonia. A later study reports that occult pneumonia is seen in only 3% of infants without respiratory findings on physical examination. Given that the risk of SBI in febrile infants and children has dropped in the era of pneumococcal vaccination and that most FWS cases will be related to urinary tract or viral infections, some authors recommend obtaining urinalysis first and considering chest imaging only if this is negative.

A group of authors combined their data with those of 2 prior studies and subjected these to a statistical meta-analysis. The larger number of patients in the combined study allowed more valid conclusions concerning the accepted practice of performing chest radiographs in febrile infants as part of the sepsis workup. These 3 series had 671 infants. In 361 infants with no clinical evidence of pulmonary disease on history and physical examination, all had normal chest radiographs. A finding of only hyperinflation on a chest radiograph was interpreted as normal because it was felt that the infants would likely have a viral illness or reactive airway disease and would not usually be receiving antibiotics, unlike older children and adults. This study indicated that a chest radiograph in a patient with no pulmonary symptoms or signs would be positive <1.2% of the time. In the current era of *S. pneumonia* and *H. flu* vaccine use, this rate might fall even further. Another study found an incidence of radiographic pneumonia in 5.3% of 2,128 children under 10 years of age with no lower respiratory symptoms (other than cough) and concluded that there was a low utility in obtaining chest radiographs in febrile children without cough. A longer duration of cough, fever, and leukocytosis increased the likelihood of radiographic pneumonia in these children.

*Variant 4: Infant or Child Aged 1 to 36 Months with FWS with Any of the Following: Respiratory Signs or Symptoms, Fever  $\geq 39^{\circ}\text{C}$ , or White Blood Cell Count  $\geq 20,000/\text{mm}^3$*

Patients with high fever, signs of respiratory distress, or white blood cell (WBC) count  $>20,000/\text{mm}^3$  are at increased risk of pneumonia; therefore, chest radiographs are indicated. The presence of rales is the single best clinical indicator of pneumonia in infants and children. Tachypnea, intercostal retractions, and nasal flaring are also predictive of pneumonia in the pediatric population. Other clinical factors that can be predictive of pneumonia in children of all ages, such as degree of fever, WBC count, and pulse oximetry, have been studied.

In a meta-analysis study, it was found that 33.2% (85/256) of the infants younger than 3 months with at least 1 clinical finding of pulmonary disease (i.e., tachypnea  $>50$  breaths/min, cyanosis,  $\text{O}_2$  saturation  $<95\%$ , rales, rhonchi, retractions, wheezing, coryza, grunting, stridor, nasal flaring, or cough) had positive chest radiographs. In a study of 510 children from 2 to 59 months of age presenting with symptoms of lower respiratory infection who had chest radiographs, 8.6% showed pneumonia. Clinical variables found to correlate with positive radiographic findings included age  $>12$  months, respiratory rate  $>50$  breaths per minute, oxygen saturation  $\leq 96\%$ , and nasal flaring in children younger than 12 months. Combinations of these clinical variables produced likelihood ratios of radiographic pneumonia from 3.6 to 11.0. In a similar study of 570 children over 1 year of age, the presence of decreased breath sounds, crackles, and tachypnea in various combinations had a high sensitivity but a poor specificity to predict pneumonia, defined as "focal infiltrates on chest radiographs." Another study found that 26% of children with fever  $\geq 39^{\circ}\text{C}$  and a WBC count  $\geq 20,000/\text{mm}^3$  had pneumonia on chest radiographs. The use of polyvalent *S. pneumonia* vaccine has been shown to reduce pneumonia with radiographic consolidation by 73%. This led one author to suggest that a chest radiograph should be obtained in patients with high fever and elevated WBC count who have not received the pneumococcal vaccine, regardless of respiratory findings. Another research group reported that since the institution of pneumococcal vaccination, the incidence of radiographically evident pneumonia has dropped by 20% to 39%. In their study of 355 children younger than 5 years with fever  $>39^{\circ}\text{C}$ , WBC count  $>20,000/\text{mm}^3$ , and respiratory symptoms, pneumonia was present in 18%, making chest radiography a reasonable study under those circumstances. Another author also recommends obtaining a chest radiograph in all patients younger than 36 months with an oxygen saturation  $<95\%$ , although there is no supporting evidence given nor are there data as to the diagnostic yield of such radiographs.

The American College of Emergency Physicians states that a chest radiograph should be considered in patients older than 3 months with fever  $\geq 39^{\circ}\text{C}$  and a WBC count  $\geq 20,000/\text{mm}^3$ . Similar recommendations have been made by the British Thoracic Society for children younger than 5 years.

*Variant 5: Child with FWS and Neutropenia*

Fever is a cause of great concern in a child with cancer or immunodeficiency who is neutropenic. In neutropenic patients, a significant fever is usually defined as a single oral temperature of  $\geq 38.3^{\circ}\text{C}$  or 2 measurements of  $\geq 38.0^{\circ}\text{C}$  at least 1 hour apart. Neutropenia is an absolute neutrophil count of  $<500/\text{mm}^3$ , or  $<1000/\text{mm}^3$  with the expectation of rapid decrease. Such children are more susceptible to the common infections facing all

children; gram-positive organisms are responsible for 70% of SBI in these patients, but gram-negative organisms are responsible for most SBI-related fatalities. These patients are also at risk for viral and other atypical infections, and invasive fungal infections are a particular concern for high-risk patients with persistent febrile neutropenia. Because of the heightened clinical concern, a chest radiograph is usually obtained in addition to other assessments, including cultures of the blood and urine.

The practice of routinely obtaining a chest radiograph has been challenged. A group of authors evaluated 54 children with cancer who were hospitalized for hundreds of episodes of fever and neutropenia. They found an incidence of radiographic pneumonia of only 3% to 6%. The children without respiratory findings had no evidence of pneumonia on chest radiographs, and children who did not have chest radiographs showed no significant outcome differences from those who did. Another group confirmed in a meta-analysis the low use of routine chest radiographs in this setting but stated that in those with a predisposition to pneumonia and those not responding to a short empiric course of antibiotics, chest radiographs should be performed despite the absence of clinical signs of a lower respiratory tract infection.

Children with neutropenia and FWS often undergo advanced imaging, but there is little evidence-based data about which studies are most efficacious. In their 2002 guidelines (not pediatric specific), the Infectious Diseases Society of America noted that one-half of febrile neutropenic patients with normal chest radiographs will have evidence of pneumonia on chest CT. One group of researchers evaluated the performance of CT in 83 neutropenic pediatric cancer patients who had 109 instances of fever lasting 4 days or more. Rates of positive CT findings varied by body region: head and neck, 8%; paranasal sinus, 41%; chest, 49%; and abdomen, 19%. Findings on paranasal sinus and chest CT led to changes in therapy in 24% and 30% of cases, respectively. However, they added that CT was rarely abnormal in the absence of localizing signs or symptoms and that in the absence of symptoms, CT findings rarely lead to therapeutic changes. A more recent study demonstrated a similar distribution of positive findings among body regions but found that only 2 of the initial positive CT scans led to a change in management (6.5% of positive scans, 0.8% of all initial scans). The authors of the study therefore recommend limiting initial empiric CT imaging to the chest only in patients without localizing signs or symptoms. Regarding the use of FDG-PET/CT, another study found a 78% sensitivity and 67% specificity in 12 of such children.

An important subset of neutropenic children are those who have undergone hematopoietic stem cell transplant. A group of researchers studied 81 hematopoietic stem cell transplant patients who had a chest radiograph performed as part of the evaluation of initial fever during transplant. None of the chest radiographs provided sufficient information for further management. In 2 of 14 episodes in patients with normal chest radiographs and in 9 of 22 episodes in patients with nonspecific chest radiographs, CT scanning resulted in a change in clinical management. Findings of large lung nodules and "halo sign" are suggestive of fungal infection.

#### *Variant 6: Infant or Child More Than 1 month of Age with Fever of Unknown Origin (FUO)*

Occult infection is the usual cause of FUO in children and is less commonly due to rheumatologic, autoimmune, neoplastic, or other inflammatory conditions. Some children never have a specific diagnosis reached. Evaluation of FUO in children is mainly based on thorough physical examination, history, and laboratory studies such as a complete blood cell count and peripheral smear, erythrocyte sedimentation rate, C-reactive protein, aerobic blood cultures, urinalysis, urine culture, tuberculin skin test, electrolytes, blood urea nitrogen, creatinine, hepatic enzymes, and human immunodeficiency virus serology. Chest radiographs are usually obtained to evaluate for occult pneumonia and lymphadenopathy. Although many studies describe the clinical course of such patients, few of them examine the utility of diagnostic imaging modalities in these difficult patients. In general, if a detailed review of the history, physical examination, and screening evaluation fail to suggest a diagnosis, more extensive imaging can be considered. This includes abdominal ultrasound (US) and CT studies of the chest, abdomen, and paranasal sinus. One research group evaluated 109 children with FUO with conventional radionuclide techniques. These studies were often positive but rarely led to an unsuspected diagnosis.

FDG-PET/CT is sensitive in detection of infection, inflammatory diseases, vasculitis, arthritis, and malignancies and was found helpful on evaluation of FUO in several adult series and meta-analysis studies. The highest yield of FDG-PET can be expected in patients with adenopathy, low hemoglobin, and increased C-reactive protein levels. There are only a few small series on the use of FDG-PET/CT in children with FUO. A group of researchers found a sensitivity of 80% and a specificity of 78% in 16 of such children. In the largest series to date, FDG-PET/CT was used in evaluation of 44 children with FUO and 33 children with unexplained signs of inflammation without fever. According to the authors, the PET findings contributed to the final diagnosis in 35 patients (45%). The study methodology is limited, with no defined selection criteria for children with FUO in whom the PET study was performed and a vague definition on the benefits of FDG-PET/CT in reaching the final diagnosis.

Whole body magnetic resonance imaging (MRI) based on inversion recovery, T1, and diffusion sequences is an evolving technique that was used in several small series in the evaluation of systemic diseases, such as multifocal osteomyelitis and tumors, but there is not yet sufficient evidence for its use for evaluation of FUO. The same applies to PET/MRI.

#### **Summary of Recommendations**

- Neonates younger than 1 month with FWS are a high-risk group; however, the yield of routine chest radiography is low in the absence of

respiratory symptoms.

- In a child with FWS, a chest radiograph should be obtained when there is clinical evidence of a respiratory illness and for those with fever  $\geq 39^{\circ}\text{C}$  or WBC count  $\geq 20,000/\text{mm}^3$ .
- In children with neutropenia and FWS, especially those after bone marrow transplant with persistent fever despite the administration of antibiotics, CT of the chest should be considered even if the chest radiograph is negative. There is lower yield for CT of the abdomen and paranasal sinus.
- Imaging studies in children with FUO have a low yield.
- More studies are needed to evaluate the potential role of FDG-PET/CT and whole-body MRI in management of children with fever.

#### Abbreviations

- CT, computed tomography
- FDG-PET, fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography
- MRI, magnetic resonance imaging
- US, ultrasound

#### Relative Radiation Level Designations

Relative Radiation Level*	Adult Effective Dose Estimate Range	Pediatric Effective Dose Estimate Range
O	0 mSv	0 mSv
<input type="text"/>	<0.1 mSv	<0.03 mSv
<input type="text"/> <input type="text"/>	0.1-1 mSv	0.03-0.3 mSv
<input type="text"/> <input type="text"/> <input type="text"/>	1-10 mSv	0.3-3 mSv
<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	10-30 mSv	3-10 mSv
<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	30-100 mSv	10-30 mSv
*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (e.g., region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as "Varies."		

## Clinical Algorithm(s)

Algorithms were not developed from criteria guidelines.

## Scope

### Disease/Condition(s)

- Fever without source (FWS)
- Fever of unknown origin (FUO)

## Guideline Category

Diagnosis

Evaluation

## Clinical Specialty



Emergency Medicine

Family Practice

Infectious Diseases

Nuclear Medicine

Pediatrics

Radiology

## Intended Users

Advanced Practice Nurses

Health Plans

Hospitals

Managed Care Organizations

Physician Assistants

Physicians

Students

Utilization Management

## Guideline Objective(s)

To evaluate the appropriateness of imaging procedures for pediatric patients with fever without source (FWS) or of unknown origin (FUO)

## Target Population

- Neonates, infants, and children with fever with or without respiratory signs or symptoms
- Children with neutropenia with no respiratory signs or symptoms

## Interventions and Practices Considered

1. X-ray, chest
2. Computed tomography (CT)
  - Chest, with contrast
  - Chest, without contrast
  - Chest, without and with contrast
  - Abdomen, with contrast
  - Abdomen, without and with contrast
  - Paranasal sinuses, with contrast
  - Paranasal sinuses, without contrast
  - Paranasal sinuses, without and with contrast
3. Fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET)/CT, skull base to mid thigh
4. Magnetic resonance imaging (MRI), whole body
  - Without contrast
  - Without and with contrast
5. Ultrasound (US), abdomen

## Major Outcomes Considered

- Utility of imaging modalities in differential diagnosis
- Sensitivity and specificity of imaging modalities to predict pneumonia

## Methodology

### Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

### Description of Methods Used to Collect/Select the Evidence

#### Literature Search Summary

Of the 79 citations in the original bibliography, 53 were retained in the final document. Articles were removed from the original bibliography if they were more than 10 years old and did not contribute to the evidence or they were no longer cited in the revised narrative text.

A new literature search was conducted in August 2013 and updated in July 2014 to identify additional evidence published since the *ACR Appropriateness Criteria® Fever without Source-Child* topic was finalized. Using the search strategies described in the literature search companion (see the "Availability of Companion Documents" field), 100 articles were found. One article was added to the bibliography. Ninety-nine articles were not used due to either poor study design, the articles were not relevant or generalizable to the topic, the results were unclear, misinterpreted, or biased, or the articles were already cited in the original bibliography.

The author added 25 citations from bibliographies, Web sites, or books that were not found in the new literature search.

### Number of Source Documents

Of the 79 citations in the original bibliography, 53 were retained in the final document. The new literature search conducted in August 2013 and updated in July 2014 identified one article that was added to the bibliography. The author added 25 citations from bibliographies, Web sites, or books that were not found in the new literature search.

### Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

### Rating Scheme for the Strength of the Evidence

#### Definitions of Study Quality Categories

Category 1 - The study is well-designed and accounts for common biases.

Category 2 - The study is moderately well-designed and accounts for most common biases.

Category 3 - The study has important study design limitations.

Category 4 - The study or source is not useful as primary evidence. The article may not be a clinical study, the study design is invalid, or conclusions are based on expert consensus.

The study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);

*Or*

The study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;

*Or*

The study is an expert opinion or consensus document.

Category M - Meta-analysis studies are not rated for study quality using the study element method because the method is designed to evaluate individual studies only. An "M" for the study quality will indicate that the study quality has not been evaluated for the meta-analysis study.

## Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

The topic author assesses the literature then drafts or revises the narrative summarizing the evidence found in the literature. American College of Radiology (ACR) staff drafts an evidence table based on the analysis of the selected literature. These tables rate the study quality for each article included in the narrative.

The expert panel reviews the narrative, evidence table and the supporting literature for each of the topic-variant combinations and assigns an appropriateness rating for each procedure listed in the variant table(s). Each individual panel member assigns a rating based on his/her interpretation of the available evidence.

More information about the evidence table development process can be found in the ACR Appropriateness Criteria® Evidence Table Development document (see the "Availability of Companion Documents" field).

## Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

## Description of Methods Used to Formulate the Recommendations

### Rating Appropriateness

The American College of Radiology (ACR) Appropriateness Criteria (AC) methodology is based on the RAND/UCLA Appropriateness Method. The appropriateness ratings for each of the procedures or treatments included in the AC topics are determined using a modified Delphi method. An initial survey is conducted to elicit each panelist's expert interpretation of the evidence, based on the available data, regarding the appropriateness of an imaging or therapeutic procedure for a specific clinical scenario. The expert panel members review the evidence presented and assess the risks or harms of doing the procedure balanced with the benefits of performing the procedure. The direct or indirect costs of a procedure are not considered as a risk or harm when determining appropriateness (additional assumptions regarding rating appropriateness can be found in the document [Rating Round Information](#) ). When the evidence for a specific topic and variant is uncertain or incomplete, expert opinion may supplement the available evidence or may be the sole source for assessing the appropriateness.

The appropriateness is represented on an ordinal scale that uses integers from 1 to 9 grouped into three categories: 1, 2, or 3 are in the category "usually not appropriate" where the harms of doing the procedure outweigh the benefits; and 7, 8, or 9 are in the category "usually appropriate" where the benefits of doing a procedure outweigh the harms or risks. The middle category, designated "may be appropriate," is represented by 4, 5, or 6 on the scale. The middle category is when the risks and benefits are equivocal or unclear, the dispersion of the individual ratings from the group median rating is too large (i.e., disagreement), the evidence is contradictory or unclear, or there are special circumstances or subpopulations which could influence the risks or benefits that are embedded in the variant.

The ratings assigned by each panel member are presented in a table displaying the frequency distribution of the ratings without identifying which members provided any particular rating. To determine the panel's recommendation, the rating category that contains the median group rating without disagreement is selected. This may be determined after either the first or second rating round. If there is disagreement after the first rating round, a conference call is scheduled to discuss the evidence and, if needed, clarify the variant or procedure description. If there is still disagreement after the second rating round, the recommendation is "may be appropriate."

This modified Delphi method enables each panelist to articulate his or her individual interpretations of the evidence or expert opinion without excessive influence from fellow panelists in a simple, standardized, and economical process. For additional information on the ratings process see the [Rating Round Information](#)  document.

Additional methodology documents, including a more detailed explanation of the complete topic development process and all ACR AC topics can be found on the [ACR Web site](#)  (see also the "Availability of Companion Documents" field).

## Rating Scheme for the Strength of the Recommendations

Not applicable

## Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

## Method of Guideline Validation

Internal Peer Review

## Description of Method of Guideline Validation

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria (AC).

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The recommendations are based on analysis of the current medical evidence literature and the application of the RAND/UCLA appropriateness method and expert panel consensus.

#### Summary of Evidence

Of the 79 references cited in the *ACR Appropriateness Criteria® Fever without Source-Child* document, 73 are categorized as diagnostic references including 1 well designed study, 3 good quality studies, and 16 quality studies that may have design limitations. Additionally, 2 references are categorized as therapeutic references including 1 well designed study. There are 54 references that may not be useful as primary evidence. There are 4 references that are meta-analysis studies.

While there are references that report on studies with design limitations, 5 well designed or good quality studies provide good evidence.

## Benefits/Harms of Implementing the Guideline Recommendations

### Potential Benefits

Selection of appropriate radiologic imaging procedures for evaluation of patients with fever without source (FWS) or of unknown origin (FUO)

## Potential Harms

### Relative Radiation Level

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, both because of organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared to those specified for adults. Additional information regarding radiation dose assessment for imaging examinations can be found in the American College of Radiology (ACR) Appropriateness Criteria® Radiation Dose Assessment Introduction document (see the "Availability of Companion Documents" field).

## Qualifying Statements

### Qualifying Statements

- The American College of Radiology (ACR) Committee on Appropriateness Criteria (AC) and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the U.S. Food and Drug Administration (FDA) have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.
- ACR seeks and encourages collaboration with other organizations on the development of the ACR AC through society representation on expert panels. Participation by representatives from collaborating societies on the expert panel does not necessarily imply individual or society endorsement of the final document.

## Implementation of the Guideline

### Description of Implementation Strategy

An implementation strategy was not provided.

## Institute of Medicine (IOM) National Healthcare Quality Report Categories

### IOM Care Need

Getting Better

### IOM Domain

## Identifying Information and Availability

### Bibliographic Source(s)

Westra SJ, Karmazyn BK, Alazraki AL, Dempsey ME, Dillman JR, Garber M, Moore SG, Raske ME, Rice HE, Rigsby CK, Safdar N, Simoneaux SF, Strouse PJ, Trout AT, Wotton-Gorges SL, Coley BD, Expert Panel on Pediatric Imaging. ACR Appropriateness Criteria® fever without source or unknown origin - child. Reston (VA): American College of Radiology (ACR); 2015. 12 p. [79 references]

### Adaptation

Not applicable: The guideline was not adapted from another source.

### Date Released

2015

### Guideline Developer(s)

American College of Radiology - Medical Specialty Society

### Source(s) of Funding

The American College of Radiology (ACR) provided the funding and the resources for these ACR Appropriateness Criteria®.

### Guideline Committee

Committee on Appropriateness Criteria, Expert Panel on Pediatric Imaging

### Composition of Group That Authored the Guideline

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### Financial Disclosures/Conflicts of Interest

Not stated

### Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Coley BD, Karmazyn B, Binkovitz LA, Bulas D, Dory CE, Garber M, Hayes LL, Keller MS, Meyer JS, Milla SS, Paidas C, Expert Panel on Pediatric Imaging. ACR Appropriateness Criteria® fever without source - child. [online publication].

Reston (VA): American College of Radiology (ACR); 2011. 9 p. [79 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Guideline Availability

Available from the [American College of Radiology \(ACR\) Web site](#) .

## Availability of Companion Documents

The following are available:

- ACR Appropriateness Criteria®. Overview. Reston (VA): American College of Radiology; 2015 Oct. 3 p. Available from the [American College of Radiology \(ACR\) Web site](#) .
- ACR Appropriateness Criteria®. Literature search process. Reston (VA): American College of Radiology; 2015 Feb. 1 p. Available from the [ACR Web site](#) .
- ACR Appropriateness Criteria®. Evidence table development. Reston (VA): American College of Radiology; 2015 Nov. 5 p. Available from the [ACR Web site](#) .
- ACR Appropriateness Criteria®. Topic development process. Reston (VA): American College of Radiology; 2015 Nov. 2 p. Available from the [ACR Web site](#) .
- ACR Appropriateness Criteria®. Rating round information. Reston (VA): American College of Radiology; 2015 Apr. 5 p. Available from the [ACR Web site](#) .
- ACR Appropriateness Criteria®. Radiation dose assessment introduction. Reston (VA): American College of Radiology; 2015 Sep. 3 p. Available from the [ACR Web site](#) .
- ACR Appropriateness Criteria®. Procedure information. Reston (VA): American College of Radiology; 2015 Feb; 2 p. Available from the [ACR Web site](#) .
- ACR Appropriateness Criteria®. Manual on contrast media. Reston (VA): American College of Radiology; 2015. 129 p. Available from the [ACR Web site](#) .
- ACR Appropriateness Criteria® fever without source or unknown origin — child. Evidence table. Reston (VA): American College of Radiology; 2015. 25 p. Available from the [ACR Web site](#) .
- ACR Appropriateness Criteria® fever without source or unknown origin — child. Literature search. Reston (VA): American College of Radiology; 2015. 2 p. Available from the [ACR Web site](#) .

## Patient Resources

None available

## NGC Status

This NGC summary was completed by ECRI on March 30, 2006. This summary was updated by ECRI Institute on July 2, 2009. This summary was updated by ECRI Institute on February 29, 2012. This summary was updated by ECRI Institute on January 29, 2016.

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